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Vital exhaustion and cardiovascular prognosis in myocardial infarction and heart failure: predictive power of different trajectories

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Background. We examined the different trajectories of vital exhaustion (VE) over a 12-month period and their impact on prognosis in a sample of myocardial infarction (MI) and chronic heart failure (CHF) patients.

Method. Consecutive MI ($n=407$) and CHF patients ($n=297$) were assessed at baseline, and at 3- and 12-month follow-up for symptoms of VE. Latent growth mixture modelling was used to examine the course of VE over time. The combined clinical endpoint was defined as cardiac hospital readmission or death.

Results. Four distinct trajectories for VE were found: low VE, decreasing VE, increasing VE, and severe VE. Sex, marital status, left ventricular ejection fraction, psychotropic medication, sample group (CHF *v.* MI) and depressive symptoms were associated with VE, varying according to classes. The mean follow-up period was 25.3 months in which 34.7% of the patients experienced an event. Multivariate Cox regression showed that, compared with patients in the low VE class, patients in the increasing VE class [hazard ratio (HR)=1.16, 95% confidence interval (CI) 1.58–3.61, $p=0.01$], and the severe VE class (HR=1.69, 95% CI 1.31–2.64, $p=0.02$) had an increased risk for adverse cardiovascular events (i.e. cardiovascular hospital readmission or cardiovascular death). Decreasing VE was not related to adverse cardiovascular events (HR=0.97, 95% CI 0.66–1.69, $p=0.81$).

Conclusions. VE trajectories varied across cardiac patients, and had a differential effect on cardiovascular outcome. Increasing VE and severe VE classes were predictors of poor cardiovascular prognosis. These results suggest that identification of cardiac patients with an increased risk of adverse health outcomes should be based on multiple assessments of VE.

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Key words: Cardiovascular outcome, depression, heart disease, vital exhaustion.

Introduction

Vital exhaustion (VE) is a frequently observed phenomenon in patients with coronary artery disease and chronic heart failure (CHF) (Appels *et al.* 1995; Pedersen & Middel, 2001; Smith *et al.* 2009). The most commonly used definition of VE is that of unusual tiredness, increased irritability, and feelings of demoralization (Appels *et al.* 1987). VE has been associated with a 2- to 3-fold increased risk of mortality and morbidity in patients with coronary artery disease (Kop *et al.* 1994; Appels *et al.* 1995; Smith *et al.* 2009), and several potential biological pathways have been

suggested which may explain this association. VE has been shown to relate to increased lipid metabolism (van Doornen & van Blokland, 1989), hypocortisolaemia (Keltikangas-Järvinen *et al.* 1996; Nicolson & van Diest, 2000), reduced fibrinolytic capacity (Kop *et al.* 1998; van Diest *et al.* 2002), parasympathetic withdrawal (Watanabe *et al.* 2002), reduced heart rate recovery after exercise (von Kanel *et al.* 2009) and increased levels of cytokines, e.g. interleukin-6 (van der Ven *et al.* 2003; Janszky *et al.* 2005).

The 21-item Maastricht Questionnaire is often used to assess VE (Appels *et al.* 1987). Previous studies have shown that VE as measured by the Maastricht Questionnaire is not similar to symptoms of fatigue, but additionally comprises factors such as depressive symptoms, sleep problems and lack of concentration (Kudielka *et al.* 2004; McGowan *et al.* 2004; Pedersen *et al.* 2007; Smith *et al.* 2009). A few other studies

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examined the overlap between VE and depressive symptoms. In a large-scale study (Kopp *et al.* 1998), VE and depressive symptoms were differently related to relevant external criteria, suggesting that the constructs are distinct from each other. Furthermore, VE and depression shared less than 40% of the variance. The latter result was confirmed by other studies (Kudielka *et al.* 2004; McGowan *et al.* 2004). VE has been shown to be prevalent in both patients with myocardial infarction (MI) and CHF patients (Appels *et al.* 2000; Smith *et al.* 2009), but it is not clear whether levels of VE differ across these patient groups. Given disease stage, VE might also be differently related to cardiovascular prognosis.

Although previous studies have stressed the importance of VE in cardiac disease (Appels & Mulder, 1988; Appels, 1990; Appels & Otten, 1992; Smith *et al.* 2009), there is a paucity of research on the evolution and/or persistence of VE. Patients may have varying courses of VE and, hence, potentially differential risks of adverse health outcomes. Knowledge of VE trajectories, their clinical and psychological characteristics, and their prognostic impact might allow for the identification of high-risk cardiac patients who may need additional clinical care above and beyond the standard medical management of the disease.

Since the course of VE has not been studied in cardiac patients, the current study's objective was to examine: (1) the course and characteristics of VE during a 12-month period and (2) their impact on cardiovascular prognosis in a combined sample of MI and CHF patients.

Method

Patients

To cover both acute and chronic cardiac disease, we combined two different samples. One sample of patients who recently had a MI was included to reflect acute cardiac disease, whereas a second sample of patients suffering from CHF was included to reflect chronic cardiac disease. This resulted in a total sample of 704 patients. The MI patients comprised 407 patients that participated in the Depression after Myocardial Infarction (DepreMI) study (Kaptein *et al.* 2006), which is a naturalistic follow-up study of the impact of depressive symptoms on cardiac prognosis in MI patients in four hospitals in the North of The Netherlands. Patients admitted for an MI between September 1997 and September 2000 were included and followed until April 2002. Inclusion criteria were: (a) chest pain for at least 20 min, (b) creatinine phosphokinase levels 100% above normal or creatinine phosphokinase-MB levels above 10%, and (c) presence

of new pathological Q waves on the electrocardiogram in at least two leads. Exclusion criteria were life expectancy of less than 1 year (because of non-cardiac condition), too poor physical condition according to hospital staff, cognitive dysfunction, inability to speak or read Dutch, occurrence of an MI in patients admitted for another reason, and follow-up visits scheduled in a non-participating hospital. Patients received usual aftercare for their MI and depressive symptoms. Of the 528 patients that were initially included, 60 patients were lost during follow-up (i.e. refusal, death), and 61 patients had missing questionnaire data on two or more measurement points, leaving 407 patients for the MI database used in the present study.

The CHF patients comprised 297 consecutive patients with systolic heart failure and a left ventricular ejection fraction (LVEF) $\leq 40\%$, visiting the heart failure out-patient clinic of the TweeSteden hospital, Tilburg, The Netherlands. Patients with diastolic heart failure, age ≥ 80 years, MI in the month prior to inclusion, other life-threatening diseases, and no or insufficient understanding of the spoken and written Dutch language were excluded beforehand. Of the 378 patients that were initially included, 44 patients died during the first year of the study, and 37 patients had missing questionnaire data on two or more measurement occasions, leaving 297 patients for the present study.

Both MI and CHF patients completed a questionnaire at baseline, 3-month follow-up and 12-month follow-up. The study protocol was approved by the institutional review boards of the participating hospitals, and was conducted conforming to the Helsinki Declaration. Every patient provided written informed consent.

VE

VE was assessed by the 21-item Maastricht Questionnaire (Appels *et al.* 1987). Each item was originally rated according to a three-point scale (yes = 0; ? = 1; no = 2), and a total score was calculated by summing the answers. The question mark was included for patients that could not decide between yes and no. The internal construct reliability of the total scale is good, with a Cronbach's α of 0.89 (Kop *et al.* 1994). Frequency analysis on every single item revealed that the question mark category was rarely used (<10%). Therefore, we decided to divide the total scores by a factor of 2 and to round up to integers at a 0.5 level. Hereby, we considered these scores as count variables of the number of VE symptoms. From a psychometric perspective, this is more appropriate than using the scores as a continuous variable. Choosing the right

variable type and subsequent underlying distribution is of particular importance for the latent class analysis (LCA) that is introduced in the statistical analyses paragraph.

Symptoms of depression

Symptoms of depression were measured by means of the Beck Depression Inventory (BDI) (Beck & Steer, 1993). Each item is rated on a 0–3 scale. A total score is obtained by summing together all the items. The BDI is a reliable and well-validated measure of depressive symptomatology (Beck *et al.* 1988), and is a widely used self-report measure of depression. This subscale was dichotomized using the standardized BDI cut-off score of ≥ 10 versus BDI scores < 10 . The correlation between VE at baseline and depressive symptoms at baseline was 0.52, and therefore share 27% of the variance.

Demographic and clinical variables

Demographic variables included sex, age (< 60 years *v.* ≥ 60 years) and marital status (partner *v.* no partner). Clinical variables comprised smoking status, LVEF ($< 40\%$ *v.* $\geq 40\%$), previous MI, diabetes mellitus and cardiac medication. Information on clinical variables was obtained from the medical records and from the treating cardiologist or heart failure nurse.

Cardiovascular prognosis

The combined clinical endpoint was defined as cardiovascular hospital readmission or cardiovascular death. Information on potential endpoints was collected from hospital records and the patients' primary care physicians. Mean follow-up duration was 25.4 months [standard deviation (S.D.) = 13.3 months].

Statistical analyses

LCA was employed to examine trajectories of VE symptoms in cardiac patients over a 12-month period (Vermunt & Magidson, 2000). A latent growth Poisson mixture model was fitted to the longitudinal VE data to identify classes of individuals following similar patterns of behaviour over time. The model assumes unobserved latent variables to explain the associations among observed scores, and can be seen as a categorical equivalent of factor analysis. One of the problems with fitting these types of latent class models is that the categorization into classes is dominated by the overall symptom levels, making it less likely that the model picks up symptom changes. A way to overcome this problem is the inclusion of a random intercept (Magidson & Vermunt, 2006).

To determine the optimal number of trajectories, Akaike's Information Criterion 3 (AIC3) was used, with a lower AIC3 indicating a better fit. However, a difference of less than 3 will favour the least complex model. Recent studies have shown that AIC3 is a better criterion than the Bayesian Information criterion and Akaike's Information Criterion in determining the number of latent classes in latent class models (Andrews & Currim, 2003; Dias, 2004).

For comparison between classes we used the χ^2 test for discrete variables. Adjusted standardized residuals (ASRs) were used to identify groups responsible for significant differences. A residual > 2.0 was taken to indicate a significantly higher frequency, and a residual < -2.0 was considered to indicate a significantly lower frequency than expected if the independence hypothesis was true (Everitt, 1977).

Multivariate Cox proportional hazards regression was used to assess whether VE trajectories predicted the combined endpoint of cardiovascular readmission or death. In the regression model, we included age, sex, marital status, smoking status, diabetes mellitus, previous MI, disease severity (LVEF), beta blockers, calcium antagonists, aspirin, psychotropics and depressive symptoms because of their relationship with cardiovascular prognosis (Gradman & Deedwania, 1994; Frasure-Smith *et al.* 1995; Wilson *et al.* 1998; Ormiston & Salpeter, 2003; Grossman & Messerli, 2004; Rumsfeld *et al.* 2005; Eaker *et al.* 2007; Kovacs & Arora, 2008). The LCA was performed with the program Latent Gold 4.5 (Vermunt & Magidson, 2000; Statistical Innovations, USA). All other data were analysed using SPSS 15.0.1 for Windows (SPSS Inc., USA). A similar approach has previously been used in MI patients (Martens *et al.* 2008), percutaneous coronary intervention (PCI) patients (Pedersen *et al.* 2008) and peripheral arterial disease (PAD) patients (Smolderen *et al.* 2008).

Results

Trajectories of VE

Fig. 1 displays the four distinct developmental trajectories for VE. AIC3 improved from one class of VE (AIC3 = 11526) to four classes of VE (AIC3 = 11315), with both the three-class model (AIC3 = 11323) and the five-class model (AIC3 = 11322) showing a significantly worse fit compared with the four-class model (AIC3 = 11315). The four-class model was therefore adopted for further analysis.

The first class (16.8% of the sample) was classified as the low VE group (intercept = 0.57, $p < 0.001$; slope = -0.06 , $p < 0.001$), and had low levels of VE on all time points. The second class (29.1%) was

Table 1. Baseline characteristics stratified by vital exhaustion class

Variable	Total	Low vital exhaustion (n = 118)	Decreasing vital exhaustion (n = 205)	Increasing vital exhaustion (n = 57)	Severe vital exhaustion (n = 324)	p
Male sex	76.6 (539)	87.3 (103) ^a	79.0 (162)	93.0 (53) ^a	68.2 (221) ^a	<0.001
Age ≥60 years	62.9 (443)	55.1 (65)	67.3 (138)	61.4 (35)	63.3 (205)	0.18
Having no partner	19.2 (135)	11.0 (13) ^a	18.0 (37)	12.3 (7)	24.1 (78) ^a	0.007
Smoking	38.2 (269)	40.7 (52)	32.7 (66)	50.9 (29)	38.9 (126)	0.06
Previous MI	29.8 (210)	21.2 (25)	31.2 (64)	22.8 (13)	33.3 (108)	0.05
Diabetes	15.2 (107)	11.9 (14)	16.1 (33)	5.3 (3)	17.6 (57)	0.07
Heart failure ^b	42.2 (297)	37.3 (44)	39.5 (81)	26.3 (15) ^a	48.5 (157) ^a	0.005
LVEF <40%	56.0 (394)	50.0 (59)	54.1 (111)	45.6 (26)	61.1 (198) ^a	0.05
Beta blockers	72.5 (510)	78.8 (93)	69.8 (143)	75.4 (43)	71.5 (231)	0.32
Calcium antagonists	17.5 (123)	19.5 (23)	16.6 (34)	19.3 (11)	17.0 (55)	0.89
Aspirin	67.3 (474)	66.1 (78)	69.3 (142)	75.4 (43)	65.1 (211)	0.42
Psychotropics	8.1 (57)	1.7 (2) ^a	4.4 (9)	1.8 (1)	6.4 (45) ^a	<0.001
Depressive symptoms	27.6 (194)	3.4 (4) ^a	9.3 (19) ^a	5.3 (3) ^a	51.9 (168) ^a	<0.001

MI, Myocardial infarction; LVEF, left ventricular ejection fraction.

Values are given as percentage (number of subjects).

^a Absolute adjusted standardized residual >2.0.

^b Chronic heart failure group as compared with the MI group.

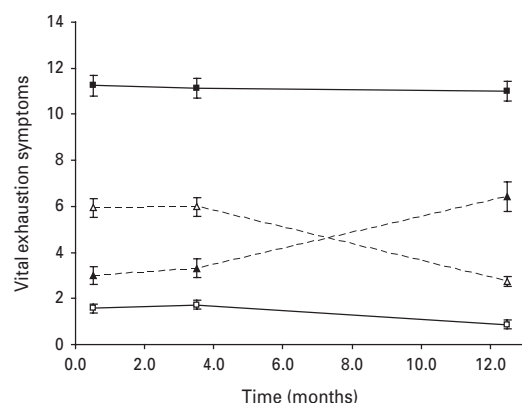


Fig. 1. Observed trajectories of vital exhaustion. —■—, Severe vital exhaustion (46.0%); —▲—, increasing vital exhaustion (8.1%); —△—, decreasing vital exhaustion (29.1%); —□—, low vital exhaustion (16.8%). Values are means, with standard deviations represented by vertical bars.

characterized by a decrease in VE symptoms over time (intercept = 1.81, $p < 0.001$; slope = -0.06 , $p < 0.001$). The third class (8.1%) was described as increasing VE (intercept = 1.30, $p < 0.001$; slope = 0.03 , $p = 0.09$). Finally, the fourth class (46.0%) was classified as severe VE (intercept = 2.38, $p < 0.001$; slope = -0.0023 , $p = 0.34$) with high levels of VE on all time points.

Characteristics of VE trajectories

There were a number of differences in demographic, clinical and psychological characteristics at baseline

as a function of VE class (Table 1). Departure from independence was most pronounced in the extreme VE groups (Table 1; denoted by footnote a), as these showed the most significant relationships with the baseline characteristics. Patients in the low VE group were more likely to be male (ASR = 3.0) and to have a partner (ASR = -2.5). In addition, they were less likely to be on psychotropics (ASR = -2.8) and to be depressed (ASR = -6.4). Patients in the decreasing VE group were less likely to be depressed (ASR = -7.0). Other deviations were not observed in this class. Patients in the increasing VE group were more likely to be male (ASR = 3.1) and to be an MI patient (Fig. 2). Furthermore, these patients were less likely to be depressed (ASR = -3.9). Finally, patients in the severe VE group were more likely to be female (ASR = -4.8), alone (ASR = 3.0), on psychotropic medication (ASR = 5.2), depressed (ASR = 13.3) and to have decreased LVEF (ASR = 2.5). As displayed in Fig. 2, CHF patients were more likely to be in the severe VE group as compared with MI patients (ASR = 3.1), independent of LVEF.

Trajectories of VE and cardiovascular prognosis

The mean follow-up period was 25.4 months (S.D. = 13.3 months). During this period, 244 patients (34.7%) experienced an adverse cardiovascular event. Lower LVEF was associated with an increased risk for adverse cardiovascular events (Table 2). Previous MI showed a trend towards significance.

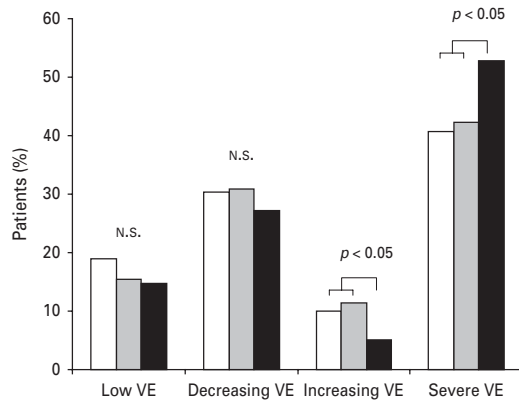


Fig. 2. Percentage of patients per vital exhaustion (VE) class stratified by sample group and left ventricular ejection fraction (LVEF). (□), Myocardial infarction (MI) + LVEF $\geq 40\%$; (▒), MI + LVEF $< 40\%$; (■), chronic heart failure (CHF). * Percentage was significantly different from that for CHF patients ($p < 0.05$).

Univariate Cox regression analysis revealed that the event rate in the increasing VE class (38.6% *v.* 22.3%, $p = 0.03$) and the severe VE class (42.9% *v.* 22.3%, $p = 0.001$) was significantly higher as compared with the low VE class. The decreasing VE class (27.3% *v.* 22.3%, $p = 0.42$) did not have a significantly different event rate as compared with the low VE class. In multivariate analysis, increasing VE and severe VE remained significant predictors of adverse cardiovascular events (Table 2). Compared with the low VE group, patients in the increasing VE class [hazard ratio (HR) = 1.16, 95% confidence interval (CI) 1.58–3.61, $p = 0.01$] and in the severe VE class (HR = 1.69, 95% CI 1.31–2.64, $p = 0.02$) had an increased risk for cardiovascular events. Patients in the decreasing VE class had a similar risk for cardiovascular events (HR = 0.97, 95% CI 0.66–1.69, $p = 0.81$) as compared with the low VE class. Adding sample group (MI *v.* CHF) as a predictor did not significantly alter the results presented in Table 2.

Trajectories versus raw scores at one time point as outcome predictors

To assess whether the trajectory model presented in Table 2 yields a better prediction of adverse outcomes as compared with using raw VE scores at single time points, the multivariable analysis was repeated three times after replacing the group bases trajectory variables with raw VE scores at, respectively, baseline, 2-month follow-up and 12-month follow-up. Raw VE scores were all independent predictors of adverse outcome in CVD patients (VE model at baseline: HR = 1.01, 95% CI 1.01–1.07, $p = 0.006$; VE model at 2-month follow-up: HR = 1.03, 95% CI 1.001–1.06,

Table 2. Trajectories of vital exhaustion and cardiac prognosis (multivariate)

Variable	HR	(95% CI)	<i>p</i>
Male sex	0.97	(0.71–1.32)	0.82
Age ≥ 60 years	1.16	(0.86–1.58)	0.33
Having no partner	0.95	(0.69–1.31)	0.76
Smoking	1.08	(0.81–1.43)	0.61
Previous MI	1.32	(0.99–1.75)	0.06
Diabetes	1.28	(0.93–1.77)	0.14
LVEF $< 40\%$	1.94	(1.36–2.75)	$< 0.001^*$
Beta blockers	0.80	(0.60–1.06)	0.13
Calcium antagonists	0.81	(0.56–1.18)	0.27
Aspirin	0.84	(0.63–1.11)	0.21
Psychotropic medication	1.26	(0.84–1.91)	0.27
Depressive symptoms	1.13	(0.82–1.54)	0.45
Decreasing vital exhaustion	1.06	(0.66–1.69)	0.81
Increasing vital exhaustion	2.04	(1.15–3.61)	0.01*
Severe vital exhaustion	1.69	(1.08–2.64)	0.02*

HR, Hazard ratio; CI, confidence interval; MI, myocardial infarction; LVEF, left ventricular ejection fraction.

* $p < 0.05$.

$p = 0.05$; VE model at 12-month follow-up: HR = 1.05, 95% CI 1.02–1.08, $p < 0.001$). Model comparison by means of a log-likelihood ratio test revealed that the trajectory model outperformed the baseline ($\chi^2 = 6.1$, $df = 2$, $p = 0.05$) and 2-month follow-up model ($\chi^2 = 9.3$, $df = 2$, $p = 0.01$), but had similar predictive power as the 12-month follow-up model ($\chi^2 = 2.5$, $df = 2$, $p = 0.29$).

Discussion

To our knowledge, this is the first study to examine the course of VE in a combined sample of MI and CHF patients. We found four distinct trajectories for VE: (i) low levels of VE at all time points; (ii) decreasing levels of VE over time; (iii) increasing levels of VE over time; (iv) high levels of VE at all time points. Sex, marital status, LVEF, psychotropic medication, sample group (CHF *v.* MI) and depressive symptoms were associated with VE, varying according to classes. Multivariate Cox regression showed that patients in the increasing VE class and in the severe VE class had an increased risk for adverse cardiovascular events as compared with patients in the low VE class, independent of covariates. Patients in the decreasing VE class had a similar risk for cardiovascular events as compared with the reference category. Finally, the group-based trajectory prediction model outperformed models with raw VE scores at baseline, and 2-month follow-up, but had similar predictive power as raw VE scores at 12-month follow-up.

The results of the present study advocate the use of latent growth mixture modelling to study the course of symptom levels over time, which has also been argued in other studies (Kaptein *et al.* 2006; Martens *et al.* 2008; Pedersen *et al.* 2008; Smolderen *et al.* 2008). Similar to our study, these investigations have also found support for multiple rather than one trajectory, although they studied depression (Kaptein *et al.* 2006; Martens *et al.* 2008; Smolderen *et al.* 2008) and anxiety (Pedersen *et al.* 2008). Our approach, however, was somewhat different from the previous studies because (1) we allowed the error terms to vary within classes which was not the case in the study of Kaptein *et al.* (2006), and (2) we included a random intercept to remove the overall response level effects (Magidson & Vermunt, 2006). In our opinion, both adjustments improved the model specification considerably, as was demonstrated by higher AIC3 values (not reported) in VE models with fixed error terms and without a random intercept.

The most important finding we feel is that two trajectories of VE were associated with an increased risk of cardiovascular events, representing chronic severely exhausted patients and patients in which levels of VE increased during the follow-up year. Of interest, MI patients were relatively more present in the increasing VE class as compared with CHF patients. Our findings thus suggest that a significant number of patients do not fully recover after an MI but deteriorate over time, which in the current study is expressed as an increase in the number of VE symptoms and subsequently an increased cardiac risk. Patients in this class might reflect a group of patients that do not respond to standard treatment procedures. These findings appear to be consistent with previous observations by Carney *et al.* (2004), de Jonge *et al.* (2007) and Kaptein *et al.* (2006) who found that persistence of depressive symptoms (despite treatment) was associated with an increased cardiac risk. Of note, in those studies depression was assessed with the BDI, in which somatic symptoms of depression (such as fatigue and sleeping difficulties) are relatively over-represented. In contrast, CHF patients were relatively more present in the severe VE class. CHF patients on average have a longer and more severe cardiac history and did not experience a recent acute coronary syndrome. CHF patients may therefore display a more stable pattern of VE over time. As a consequence, the most vulnerable class of CHF patients is characterized by a chronic, severe level of VE. Thus, the most vulnerable MI and CHF patients may differ in their patterns of VE.

Notably, the two VE trajectories predicted cardiac outcome independent of depression symptoms at baseline. This either could mean that depression and

VE are related, but not similar, constructs that relate to cardiac outcome because of different reasons, but also could indicate that the VE trajectories give a more precise indication of the status of the patient, as a time factor is included, making it a better predictor of cardiac outcome. The first explanation is supported by our previous findings that the VE symptom clusters of fatigue and cognitive-affective depressive symptoms were responsible for having a poorer health status (Smith *et al.* 2009).

From a clinical point of view, knowledge about factors characterizing trajectories that display changes over time is important as they point to targets for intervention. Importantly, the findings of the present study indicate that VE trajectories are differently related to an increase of adverse cardiovascular events. In a previous study, we have shown that symptom profiles of VE in CHF patients, measured at a single time point, were associated with rehospitalization (Smith *et al.* 2009). It would be interesting to study these symptom profiles using a latent growth mixture modelling approach, and examine the effect of symptom profile trajectories on cardiovascular prognosis. Furthermore, in the multivariate Cox model, we controlled for depressive symptoms measured at baseline, and demonstrated that trajectories of VE independently predicted our outcome measure. The potential effects of depressive symptoms at later time points were ignored. It would be worthwhile to investigate the distinctiveness of VE and depression using a joint trajectory modelling approach (Jones & Nagin, 2005), providing full control of each other's effects on outcome measures. Generally, large-scale studies should give a more in-depth insight into the differential effect of the VE trajectories on cardiovascular prognosis.

The results of the present study might help to guide future interventions. It is important to note that results from the EXhaustion Intervention Trial (EXIT) showed that VE was influenced by the intervention depending upon a prior history of coronary artery disease (CAD) (Appels *et al.* 2006). Since this study included patients with CAD (previous MI) and CHF, it should be taken into account that interventions might not equally benefit the course of these two cardiac diseases.

This study has a number of limitations. First, only the patients who lived to the end of the assessment process were included in the study. This may have introduced potential selection bias, and may under- or overestimate the effects of VE found in this study. Second, the cardiologist or heart failure nurses asked patients to participate in the study, and this interaction pattern might have influenced patient selection. Third, the examined predictors of the VE trajectories were only assessed once. Given that, for example,

depressive symptoms were identified as an independent predictor of persistent VE, it is possible that these levels may be attributed to persistent depressive symptoms, rather than baseline levels. Fourth, we were not able to control for some potentially important variables in the multivariable analyses as a result of combining two databases that did not fully match [e.g. blood pressure, body mass index, physical exercise, alcohol consumption, severity of MI, angiotensin-converting enzyme (ACE) inhibitors]. Nevertheless, the strengths of the current study were the repeated assessment of VE over time, the prospective design examining the course of VE over time using a state-of-the-art modelling approach, and the use of a semi-objective medical outcome. Finally, we used a reliable and valid measure of VE.

In summary, we found four distinct trajectories for VE. Several predictors, varying according to classes, could be identified, with sex, marital status, LVEF, psychotropic medication, sample group (CHF *v.* MI) and depressive symptoms being the most prominent ones. Increasing VE class and the severe VE class had an increased risk for adverse cardiovascular events as compared with the low VE class. Patients in the decreasing VE class did not have an increased risk for adverse events as compared with the reference category.

Future studies are warranted to confirm these findings, given that this was the first study to examine the course of VE in cardiac patients. The results of the present study may help identify distinct groups of patients with potentially differential risks of adverse health outcomes, guide future interventions, and therefore be valuable for both research and clinical practice.

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Declaration of Interest

None.

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